Remarks / Arguments

I. Status of the Claims

Claims 1-5, 7-9, and 24-35 are pending in this application.

II. Rejections Under 35 U.S.C. 112, 1st Paragraph (enablement)

Claims 24-35 stand rejected under 35 U.S.C. 112, 1st paragraph, as lacking enablement in the specification. The Examiner has stated:

> [T]he specification . . . does not reasonably provide enablement for a method for making a tissue engineering scaffold using any matrix-enhancing molecule, any matrix-enhancing molecule such as TGF beta, angiotensin II, insulin like growth factor and ascorbic acid at any concentration sufficient to elicit production of any extracellular matrix by any cell, any cell such as smooth muscle cells, endothelial cells, fibroblasts, chondrocytes, and any combination thereof attached to any engineering scaffold without increasing cellular proliferaton of the attached cells as set forth in claims 24-35.
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> . . .
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> The specification discloses only TGF beta at optimal concentration in the range of between one and five ng TGF-β/ml, which is equivalent to between 4×10^{-6} and 4×10^{-3} nmol/ml covalently coupled to hydrogel via polyethylene glycol for inducing extracellular matrix production by aortic smooth muscle cells.
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> The specification does not teach how to make all "matrix-enhancing molecule" for the claimed method without the amino acid sequence. Given the unlimited number of matrix enhancing molecules, there is insufficient guidance as to which matrix enhancing molecules would induce the production of which extracellular matrix by which cell type without increasing cellular proliferation of the attached cells to the scaffold, much less at which particular concentration for the claimed method. Further, there is insufficient working example showing that any matrix enhancing molecule is effective for inducing matrix production in all cell type, in turn, would be useful for implantation. The specification does not teach how to predict which matrix-enhancing molecule is effective for inducing matrix production by which cell type.
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> . . .

> Given the unlimited number of matrix enhancing molecules and without the structure (i.e., chemical structure of amino acid sequence), it is unpredictable which undisclosed matrix-enhancing molecule at which concentration is effective for inducing which matrix production for the claimed method.

(Office Action, at 2-3.) Applicants respectfully traverse the enablement rejection. The claimed invention must be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F2d. at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). Evaluation of undue experimentation involves, but is not limited to the following factors: breadth of the claims, nature of the invention, state of the prior art, level of one of ordinary skill, level of predictability, amount of direction provided by the inventor, existence of working examples and the quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F2d. at 731, 8 USPQ2d at 1400 (Fed. Cir. 1988). Applicants respectfully assert that the specification provides sufficient disclosure to enable one of skill in the art to make and use the invention.

A. Applicants' independent claim 24 is enabled

With respect to the matrix-enhancing molecule, the Examiner has stated:

> The specification does not teach how to make all "matrix-enhancing molecule" for the claimed method without the amino acid sequence. Given the unlimited number of matrix enhancing molecules, there is insufficient guidance as to which matrix enhancing molecules would induce the production of which extracellular matrix by which cell type without increasing cellular proliferation of the attached cells to the scaffold, much less at which particular concentration for the claimed method. Further, there is insufficient working example showing that any matrix enhancing molecule is effective for inducing matrix production in all cell type, in turn, would be useful for implantation. The specification does not teach how to predict which matrix-enhancing molecule is effective for inducing matrix production by which cell type.

(Office Action, at 3.) Applicants respectfully disagree.

1. Enablement does not require the amino acid sequences of matrix-enhancing molecules

With respect to the amino acid sequence of matrix-enhancing molecules, the Examiner has stated that

> The specification does not teach how to make all "matrix-enhancing molecule" for the claimed method without the amino acid sequence.

(Office Action at 3.) The Examiner's statement with regard to the amino acid sequence of matrix-enhancing molecules has no bearing on enablement of the claims. A skilled artisan does not need to know the amino acid sequence of a particular matrix-enhancing molecule to make and use the claimed methods. In fact, some matrix-enhancing molecules do not even have an amino acid sequence, for example, ascorbic acid.

2. Applicants have enabled matrix-enhancing molecules

With respect to the matrix-enhancing molecules, the Examiner has stated that:

> Given the unlimited number of matrix enhancing molecules, there is insufficient guidance as to which matrix enhancing molecules would induce the production of which extracellular matrix by which cell type without increasing cellular proliferation of the attached cells to the scaffold, much less at which particular concentration for the claimed method.

(Office Action at 3.) Applicants respectfully disagree. One source of guidance may be found in Applicants' independent claim 24 itself, which recites that "the matrix-enhancing molecule . . . elicit[s] production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell." *See* MPEP 2164 ("[W]hen the subject matter is not in the specification portion of the application as filed but is in the claims, the limitation in and of itself may enable one skilled in the art to make and use the claim containing the limitation."). Moreover, suitable matrix-enhancing molecules will be recognizable to those of ordinary skill in the art, with the benefit of Applicants' disclosure. *See* MPEP § 2164.05(a) ("The specification need not disclose what is well known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public." (citations omitted)) To aid in such determination, Applicants' disclosure provides examples of four suitable matrix enhancing molecules. *See* Application ¶ 27-29. Moreover, suitable matrix-enhancing molecules are well known in the art, as the art cited by the Examiner shows. *See, e.g.*, '430 Patent, col. 6, ll. 55-66;'849 Patent, col. 16, Table 1.

Regarding guidance for "which extracellular matrix," such is provided by Applicants' specification, as well as by what well known to those skilled in the art. First, Applicants'

specification provides examples of extracellular matrix components. Application ¶ 28. And the extracellular matrix has been well characterized, as the art cited by the Examiner shows. *See, e.g.*,'849 Patent, col. 14, ll. 31-39.

Regarding guidance for "which cell type," such is provided by Applicants' specification, as well as by what well known to those skilled in the art. First, Applicants' specification provides examples of various cell types, as well as sources for such cells. Application ¶ 35-38. And the use of various cell types is well known in the art, as the art cited by the Examiner shows. *See, e.g.*, '849 Patent, col. 16, Table 1.

Regarding guidance for "without increasing cellular proliferation of the attached cells to the scaffold," such is provided by Applicants' claims and specification, as well as by what is well known to those skilled in the art. First, claim 24 itself provides guidance because it recites that "the matrix-enhancing molecule . . . elicit[s] production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell." *See* MPEP 2164. Likewise, the specification describes "[m]atrix-enhancing molecules which promote increased production of ECM . . . without substantially increasing cell proliferation." Application ¶ 28. Further, the specification provides examples of suitable matrix-enhancing molecules: "These matrix-enhancing molecules include TGF-β, angiotensin II, insulin-like growth factors and ascorbic acid." Application ¶ 28. The TGF-β species is described in detail, *see* Application ¶ 29, 43-77, as is the ascorbic acid species, *see* Application ¶ 78-79. Taken together, the examples of suitable matrix-enhancing molecules, detailed descriptions of these molecules, and express recitation by the claims are enabling. Nevertheless, guidance is also provided by the knowledge well known in the art, as the art cited by the Examiner shows. *See, e.g.*, Dinbergs, et al., J. Biol. Chem. 271(47): 29822-29 (1996); Scott-Burden, et al., J. Cardiovasc. Pharmacol. 16 Suppl 4: S36-41 (1990); '849 Patent, col. 16, Table 1; *Id.* col. 15, ll. 25-28 ("Various growth factors or chemical compounds, including those discussed supra, may be added to the ECM components to control the growth and differentiation cells.").

3. Applicants have enabled concentrations of matrix-enhancing molecules

Regarding guidance for "at which particular concentration for the claimed method," such is provided by Applicants' claims and specification, as well as by what is well known to those skilled in the art. First, the claim language itself provides the concentration of the matrix-

enhancing molecule: "sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell." *See* MPEP 2164. Applicants' specification also describes that "[t]he optimal density [of the matrix-enhancing molecule] will depend on the type of cells to be attached to the scaffold." Application ¶ 34. Additionally, the specification provides examples of suitable concentrations of specific matrix-enhancing molecules to use with a specific cell type. *See* MPEP § 2164.06(b) (providing the example of *In re Bundy*, 642 F.2d 430, 434 (C.C.P.A. 1981), where even though the specification lacked examples of specific dosages, it did teach that the claimed compositions had certain properties and activities similar to related known compositions and therefore was enabled).

The specification teaches how a skilled person could determine a particular concentration with reference to TGF-β and ascorbic acid. *See* Application ¶ 29, 43-77-79. Furthermore, Applicants respectfully submit that the determination of a particular concentration of a particular matrix-enhancing molecule does not require testing that is unduly burdensome, in part because it is known within the art the approximate range of concentrations in which various matrix-enhancing molecules are useful in soluble form. This provides a starting point for those of ordinary skill to begin performing a reasonable amount of experimentation to identify an effective density for the matrix-enhancing molecule of interest in tethered form.

Furthermore, Applicants' disclosure sets forth exemplary procedures for conducting such experimentation, which further militates against terming such experimentation "undue." *See* Application, "Examples 1-4." Such reasonable experimentation is permissible under 35 U.S.C. § 112, because enablement does not hinge on whether *any* experimentation is necessary, but only on whether any such experimentation may be termed "undue." MPEP §2164.06 ("'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" (citations omitted). Where, as here, those of ordinary skill in the art typically engage in some degree of experimentation, such experimentation should not be considered undue. Here, Applicants have provided sufficient disclosure that those of skill in the art, with the benefit of Applicants' disclosure, will be able to determine, after reasonable experimentation, suitable "matrix-

enhancing molecules" and the "concentration" of a particular matrix-enhancing molecule to use to practice the claimed invention.

B. Experimentation, if required, would not be "undue"

The Examiner has also stated:

> Further, there is insufficient working example showing that any matrix enhancing molecule is effective for inducing matrix production in all cell type, in turn, would be useful for implantation. The specification does not teach how to predict which matrix-enhancing molecule is effective for inducing matrix production by which cell type.

(Office Action, at 3.) Applicants respectfully disagree because Applicants' specification provides working examples, and to the extent any experimentation is needed, a skilled person would not consider it undue.

Applicants' specification, through the cited examples, also provides a very detailed description of two species of matrix-enhancing molecules, TGF-β and ascorbic acid. As discussed above, these examples describe how to test different matrix-enhancing molecules to determine, among other things, suitable cells and concentrations. The specification provides very detailed descriptions of ways to determine if the desired results have been obtained. Further, such experimentation as may be performed to identify all concentrations for matrix-enhancing molecules meeting the claim limitations merely involves trying new molecules using methods that are well-known or described in the specification. Moreover, the level of skill in the art further contradicts the Examiner's statement regarding whether any experimentation would be termed "undue." *See, e.g.*, '849 Patent, col. 17, ll. 60-63 ("One of ordinary skill can readily screen a cell type to determine its responsiveness to an ECM molecule or to a cellular ECM from a specific source, to determine its effectiveness in controlling cell distribution."). Further, Applicants submit that based on the data that Applicants have provided for TGF-β and ascorbic acid, one skilled in the art would also expect other matrix-enhancing molecules to be operable.

C. Conclusion

Applicants submit that given the knowledge of the skilled artisan and the teachings of the present specification, claims 24-35 are enabled. Applicants respectfully request withdrawal of this rejection with respect to claims 24-35, and further request the timely issuance of a Notice of Allowance for these claims.

III. Rejections Under 35 U.S.C. 112, 1st Paragraph (possession of invention)

Claims 24-35 stand rejected under 35 U.S.C. 112, 1st paragraph, as containing subject matter not described in the specification in a manner that reasonably conveys to one skilled in the art that Applicants possessed the claimed invention at the time of filing the application. The Examiner has stated, in pertinent part:

> The specification does not reasonably provide a written description of (1) any matrix-enhancing molecule, any matrix-enhancing molecule such as TGF beta, angiotensin II, insulin like growth factor and ascorbic [acid] at any concentration sufficient to elicit production of (2) any extracellular matrix by (3) any cell attached to any engineering scaffold.
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> The specification discloses only TGF beta at optimal concentration in the range of between one and five ng TGF-β/ml, which is equivalent to between 4 x 10^{-6} and 4 x 10^{-3} nmol/ml covalently coupled to hydrogel via polyethylene glycol for inducing extracellular matrix production by aortic smooth muscle cells.
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> With the exception of the specific matrix-enhancing molecule to eliciting matrix production in only smooth muscle cells for the claimed method, there is insufficient written description about the structure associated with function of all matrix-enhancing molecule to induce matrix production in any other cells for the claimed method. Given the unlimited number of matrix-enhancing molecule, the concentration effective for each undisclosed matrix-enhancing molecule for which cell type for the claimed method is not adequately described.
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> The specification discloses only a method of making tissue engineering scaffold using only TGF beta covalently coupled to PEG-diacrylate hydrogel, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of matrix-enhancing molecule to describe the genus for the claimed method. This, Applicant was not in possession of the claimed genus.

(Office Action, at 4.) Applicants respectfully traverse. An application's written description is "presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to rebut the presumption." MPEP § 2163.04. The burden falls on the Examiner to establish a "reasonable basis to challenge the adequacy of the written description." MPEP § 2163.04. "The subject matter of the claim need not be described literally

in order for the disclosure to satisfy the description requirement." MPEP § 2163.02. A specification that conveys "with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed" satisfies the written description requirement. MPEP § 2163.02. The Examiner must present evidence of "why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." MPEP § 2163.04. Applicants respectfully assert that the Examiner has not met the burden of demonstrating why a person of ordinary skill in the art would not recognize in Applicants' disclosure a description of "a method for making a tissue engineering scaffold" as recited by Applicants' independent claim 24. *See* MPEP § 2163(II)(A)(3)(b).

A. Applicants have described matrix-enhancing molecules

Applicants' specification adequately describes matrix-enhancing molecules. For example, Applicants' specification states that "[m]atrix-enhancing molecules which promote increased production of ECM can be attached to the scaffold material to induce production of matrix proteins . . . without substantially increasing cell proliferation. These matrix-enhancing molecules include TGF-β, angiotensin II, insulin-like growth factors and ascorbic acid." Application ¶ 28. Applicant's specification also discloses that the concentration for a specific matrix-enhancing molecule "will depend on the type of cell to be attached to the scaffold." Application ¶ 34. Moreover, Applicant's specification provides exemplary concentrations of matrix-enhancing molecules. For example, the concentration of the matrix-enhancing molecule TGF-β needed to elicit ECM production in auricular chondrocytes is provided. Application ¶ 34. As another example, the concentration of another specific matrix-enhancing molecule that is sufficient to produce ECM in aortic smooth muscle cells and auricular chondrocytes is also provided. Application ¶ 78-79. Furthermore, independent claim 24 specifically recites the concentration of the matrix-enhancing molecule: "the matrix-enhancing molecule is present at a concentration sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell."

Applicants further note that suitable matrix-enhancing molecules are well known in the art, as the art cited by the Examiner shows. See, e.g., '430 Patent, col. 6, ll. 55-66; '849 Patent, col. 16, Table 1. Thus, suitable matrix-enhancing molecules will be recognizable to those of ordinary skill in the art, with the benefit of Applicants' disclosure. See MPEP § 2164.05(a)

("The specification need not disclose what is well known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public." (citations omitted)).

B. Applicants have described extracellular matrix

Applicants' specification sufficiently describes extracellular matrix. Applicants' specification states that ECM includes "matrix proteins, such as glycoproteins, elastin, and collagen." Application, ¶ 28. The specification explains that "[i]n order to maintain proper mechanical integrity of the tissue, the cells must generate sufficient extracellular matrix (ECM)." Application ¶ 4. Furthermore, the specification describes how to evaluate matrix protein production, including the composition of the ECM. Application ¶ 51-53, 62. In addition to the disclosure provided by Applicants' specification, persons skilled in the art recognize that the extracellular matrix is well characterized, as the art cited by the Examiner shows. See, e.g.,'849 Patent, col. 14, ll. 31-39.

C. Applicants have described cells attached to the scaffold.

Applicants' specification adequately describes cells attached to the scaffold. Applicants describe a number of suitable cells and cell sources. For example, the specification states that "[p]referred cells for formation of vascular tissue include smooth muscle cells, endothelial cells, and fibroblasts. Preferred cells for formation of connective tissue include chondrocytes, fibroblasts, and other types of cells that differentiate into bone or cartilage." Application, ¶ 38. Furthermore, the use of various cell types is well known in the art, as the art cited by the Examiner shows. See, e.g., '849 Patent, col. 16, Table 1.

D. Applicants have described scaffolds

Applicants' specification states that "[m]atrix-enhancing molecules which promote increased production of ECM can be attached to the scaffold material to induce production of matrix proteins . . . without substantially increasing cell proliferation. These matrix-enhancing molecules include TGF-β, angiotensin II, insulin-like growth factors and ascorbic acid." Application ¶ 28. Applicants' specification also discloses that the concentration for a specific matrix-enhancing molecule "will depend on the type of cell to be attached to the scaffold." Application ¶ 34. In connection, the description provides an example of a specific matrix-enhancing molecule, the concentration needed to elicit ECM production, and the specific type of

cell that produces the ECM. Application ¶ 34. Moreover, the examples describe other examples of matrix-enhancing molecules (Application ¶ 78-79), concentrations (Application ¶ 76-79), and cells (Application ¶ 71, 74, and 76).

E. Applicants have described the correlation of structure and function

Throughout Applicants' specification and claims, the relationship between the structure of a matrix-enhancing molecule and its function is described. In short, the matrix-enhancing molecule is covalently coupled to the scaffold through a tether. This structure-function relationship is expressly recited in the claims. For example, Applicants' independent claim 24 itself recites "covalently coupling the matrix-enhancing molecule to the scaffold, wherein the matrix-enhancing molecule is present at a concentration sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell." Likewise, Applicants' specification provides that "[m]atrix-enhancing molecules which promote increased production of ECM . . . without substantially increasing cell proliferation." Application ¶ 28. And Applicants' specification further describes that "[f]or the matrix-enhancing molecules to induce formation of ECM, it is necessary for the molecule to be tethered to the scaffold by a tether." Application ¶ 32. Applicants' specification also describes that "[t]he optimal density [of the matrix-enhancing molecule] will depend on the type of cells to be attached to the scaffold." Application ¶ 34. Additionally, Applicants' specification provides examples of suitable concentrations of specific matrix-enhancing molecules to use with a specific cell type, as well as how a skilled person could determine a particular concentration with reference to TGF-β and ascorbic acid. See Application ¶ 29, 43-77-79.

Accordingly, Applicants' claims and specification expressly provide a correlation between the structure of the matrix-enhancing molecule (i.e., tethered to a scaffold), and function of the matrix-enhancing molecule (i.e., elicit production of extracellular matrix without increasing cellular proliferation). Moreover, Applicants note that suitable matrix-enhancing molecules and their effects on cells are well known in the art, as the art cited by the Examiner shows. See, e.g., '430 Patent, col. 6, ll. 55-66; '849 Patent, col. 16, Table 1; Id. , col. 14, ll. 31-39; Id. col. 15, ll. 25-28; Dinbergs, et al., J. Biol. Chem. 271(47): 29822-29 (1996); Scott-Burden, et al., J. Cardiovasc. Pharmacol. 16 Suppl 4: S36-41 (1990). "[T]he written description requirement may be satisfied through disclosure of function and minimal structure when there is

a well-established correlation between structure and function." MPEP § 2163(II)(A)(3)(a)(i). Thus, for these reasons alone, Applicants have satisfied the written description requirement.

F. Applicants have described representative species

Applicants have provided examples of suitable matrix-enhancing molecules: "These matrix-enhancing molecules include TGF-β, angiotensin II, insulin-like growth factors and ascorbic acid." Application ¶ 28. The TGF-β species is described in detail, see Application ¶ 29, 43-77, as is the ascorbic acid species, see Application ¶ 78-79. In view of the knowledge of skilled persons and the species disclosed, Applicants respectfully submit that persons of skill in the art would recognize that Applicants were in possession of the necessary common attributes possessed by matrix-enhancing molecules as claimed in Applicants' claims 24-35. See MPEP § 2163(II)(A)(3)(a)(ii) ("Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.").

G. Conclusion

Applicants respectfully submit that the above-cited portions of applicants' specification, along with the rest of the application, are sufficient to convey to one skilled in the art that, as of the filing date, applicants were in possession of the invention as claimed.

As noted above, an application's written description is "presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to rebut the presumption," MPEP § 2163.04, and the burden falls on the Examiner to establish a "reasonable basis to challenge the adequacy of the written description." *Id.* "The subject matter of the claim need not be described literally in order for the disclosure to satisfy the description requirement," but instead, a specification that conveys "with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed" satisfies the written description requirement. MPEP § 2163.02. The Examiner must present evidence of "why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." MPEP § 2163.04. Particularly in view of the fact that Applicants' specification describes matrix-enhancing molecules, concentrations sufficient to elicit ECM production, and types of cell that produces the ECM, Applicants respectfully assert that the Examiner has not adequately explained why Applicants'

written description fails to convey to those skilled in the art that, as of the filing date, applicant was in possession of the invention as claimed. Applicants respectfully assert that the Examiner has not met her initial burden "of presenting evidence by a preponderance of evidence why a person skilled in the art would not recognize" in the present application, a description of the invention as defined by the claims. Consequently, Applicants respectfully request withdrawal of the rejection of claims 24-35, and the timely issuance of a notice of allowance therefor.

IV. Rejection of Certain Claims Under 35 U.S.C. § 102(b) as Anticipated by U.S. Patent No. 5,162,430 (the '430 Patent)

Claims 24, 28, 31 and 35 stand rejected under 35 U.S.C. 102(b) as anticipated by U.S. Patent No. 5,162,430. In this regard, the Examiner has stated:

> The '430 patent teaches a method of making a tissue engineering scaffold by providing a scaffold such as collagen (col. 4, lines 5-6, in particular) covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol (see PEG, col. 5, lines 32-55, in particular) covalently coupled to a matrix enhancing molecule such as TGFbeta (col. 6, line 58, see entire document, col. 8, General Method, Examples 1 and 6, col. 19, in particular) or insulin like growth factor or combination thereof (see col 6, line 63, in particular). The reference polyethylene glycol has a molecular weight of between 1900, and about 8,000, which is between the claimed 200 and 10,000 (see col. 5, line 39, in particular). The reference tissue engineering is useful for tissue or organ implantation or tissue regeneration (see col. 4, line 28-40, in particular). Thus, the reference teachings anticipate the claimed invention.

(Office Action, at 5.) Applicants respectfully traverse the rejection for the reasons discussed below.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP § 2131. In addition, "[t]he elements must be arranged as required by the claim." M.P.E.P. § 2131. Applicants respectfully assert that the Examiner has not shown that the '430 Patent discloses, teaches, or suggests, either expressly or inherently, that "the matrix-enhancing molecule is present at a concentration sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell," as recited in Applicants' independent claim 24.

The '430 Patent is directed to a collagen-polymer conjugate. '430 Patent, col. 4, ll. 5-6. The '430 Patent teaches that such compositions may be used to treat "defects due to loss or absence of soft tissue or soft tissue support, or to loss of bone." '430 Patent, col. 6, ll. 28-32. In connection, "biologically active factors to aid in healing or regrowth of normal tissue" may be chemically linked to a collagen-polymer composition. '430 Patent, col. 6, l. 53-col. 7, l. 5. The biologically active factor is present at a concentration sufficient "to stimulate tissue growth to a detectable degree[, and] [t]issue, in this context, includes connective tissue, bone, cartilage, epidermis and dermis, blood, and other tissue." '430 Patent, col. 7, ll. 17-22. Nowhere, however, has the '430 Patent been shown to teach or suggest "a concentration sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell," as recited in Applicants' independent claim 24.

For at least these reasons, Applicants submit that claims 24-35 have not been shown to be anticipated by the '430 Patent. Accordingly, Applicants respectfully request withdrawal of this rejection with respect to claims 24-35 and further request the timely issuance of a Notice of Allowance for these claims.

V. Rejection of Certain Claims Under 35 U.S.C. § 103 as Unpatentable Over the '430 Patent In View of *Dinbergs*

Claims 1-2, 4, 8 and 9 stand rejected under 35 U.S.C. 103 as unpatentable over the '430 Patent in view of the *Dinbergs* reference (J. Biol. Chem. 271(47): 29822-29, 1996). In asserting these rejections, the Examiner describes the alleged teachings of the '430 Patent as printed above in Section 4, and further states, in pertinent part:

> The claimed invention in claim 1 differs from the reference only in that the method wherein the TGF-beta is present at a density of between 1 and 100 ng/ml or in a concentration of between about $4x10^{-6}$ and $4x10^{-3}$ nmol/ml.
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> Dinbergs *et al* teach a method for making a tissue engineering scaffold such as alginate/heparin-sepharose microsphere for inducing formation of extracellular matrix by cells such as endothelial cells and smooth muscle cells bound to said scaffold comprising coupling various matrix-enhancing molecule such as bFGF or TGFβ in a concentration 1-10 ng/ml (See Alginate/Heparin-Sepharose Microsphere Preparation and Growth Factor Incorporation, page 29823, column 2, bridging page 29824 column 1, in particular). The reference TGFβ is effective to elicit

> production of extracellular matrix (see page 29822, column 2, last paragraph, in particular) without increasing cellular proliferation (See Fig 2B, Fig 3B, Abstract, in particular). Dinbergs *et* al teach TGFβ has been incorporated into scaffold or various biodegradable polymer matrix such as collagen, hydrogel such as alginate, hydron (hyaluronic acid) and polyethylene glycol polymers (See page 29827, column 2, first full paragraph, in particular). Dinbergs *et al* teach TGFβ is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig. 3A, in particular).
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> Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use TGFbeta at a concentration of 1-10 ng/ml as taught by Dinbergs *et al* for a method of making a tissue engineering scaffold for inducing formation of extracellular matrix by cells such as smooth muscle cell or endothelial cells where the TGF is covalently coupled to collagen or alginate via a polymer tethered as taught by the '430 patent and Dinbergs *et al.*

(Office Action, at 6-7.) Applicants respectfully traverse.

As an initial matter, Applicants respectfully submit that the proposed combination of the '430 Patent with *Dinbergs* is improper, because the Examiner has not provided a sufficient teaching, suggestion, or motivation in the prior art to make such a combination. A combination of prior art references can obviate a claim under 35 U.S.C. 103 "only . . . by combining . . . the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." MPEP §2143.01. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *Id.* (citation omitted). "The teaching or suggestion to make the claimed combination . . . must . . . be found in the prior art, not in applicant's disclosure." MPEP 2143. Moreover, "the mere fact that references can be combined . . . does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP 2143.01 (emphasis in original). Applicants respectfully submit that the Examiner has not provided the requisite teaching, suggestion or motivation in the prior art to make the proposed combination.

Applicants further submit that an ordinary artisan acting at the time of Applicants' invention would not have had a reasonable expectation that the proposed '430 Patent-*Dinbergs* combination would succeed. Finally, Applicant asserts that the Examiner has not considered the cited references and Applicants' invention as a whole, and therefore used improper hindsight reconstruction to make the proposed '430 Patent-*Dinbergs* combination, which the MPEP and the governing Federal Circuit case law prohibit.

A. The Examiner has not shown a sufficient suggestion or motivation in the prior art or among those skilled in the art to combine the teachings of the '430 Patent and *Dinbergs*

There must be a basis in the prior art to properly modify or combine reference teachings. MPEP § 2143. Accordingly, even if all elements of a claim are disclosed in various prior art references, the claimed invention taken as a whole cannot be said to be obvious without some reason given in the prior art why one of ordinary skill in the art at the time of the invention would have been prompted to modify the teachings of a reference, or combine the teachings of multiple references, to arrive at the claimed invention. Here, the Examiner has shown no suggestion or motivation to combine the '430 Patent and *Dinbergs*, and Applicants further assert that the proposed combination would change the principle of operation of both the '430 Patent and *Dinbergs*. MPEP §2143.01.

The '430 Patent teaches that "biologically active factors," like TGF-β, can be chemically linked to a collagen-polymer conjugate to "aid in healing or regrowth of normal tissue." '430 Patent, col. 6, ll. 54-55. "Compositions of the invention which contain growth factors are particularly suited for sustained administration of factors, as in the case of wound healing promotion. Osteoinductive factors and cofactors (including TGF-β) may be advantageously incorporated into compositions destined for bone replacement, augmentation, and/or defect repair." '430 Patent, col. 12, l. 63-col. 13, l. 1; '430 Patent, 4, ll. 34-41 ("Such tethering of growth factors to collagen molecules provides an effective slow-release drug delivery system.") The growth factors are used at concentrations sufficient to "stimulate tissue growth to a detectable degree." '430 Patent, col. 7, ll. 18-22.

Dinbergs teaches that growth factors, like TGF-β, may be released by various polymer devices to regulate cell growth. *Dinbergs* at 29827. In connection, *Dinbergs* teaches that the naturally occurring release rate for a given growth factor should be considered when choosing

the rate to deliver growth factors to cells. *See Dinbergs* at 29826. For TGF-β in particular, *Dinbergs* showed that sustained release from a microsphere was better at inhibiting proliferation of smooth muscle cells. *Dinbergs* at 29822-3.

In light of these teachings, a combination of the '430 Patent and *Dinbergs* would change the basic principle under which each of the '430 Patent was designed to operate. The '430 Patent was designed for sustained release of growth factors, such as TGF-β, to "stimulate tissue growth to a detectable degree." '430 Patent, col. 7, ll. 18-22; col. 19, ll. 10-56 and Figure 2. But according to *Dinbergs*, the slow release of TGF-β would actually inhibit cellular proliferation, preventing tissue growth to a detectable degree. Therefore, there would be no motivation to combine the teachings of the '430 Patent and *Dinbergs*. For at least these reasons, Applicants respectfully submit that the combination of the '430 Patent and *Dinbergs* is improper.

B. The proposed combination of the '430 Patent and *Dinbergs* has not been shown to lead to a reasonable expectation of success

Not only does the above-described incompatibility of the '430 Patent with *Dinbergs* preclude a suggestion or motivation to combine, but it also signifies that an ordinary artisan would not have reasonably expected that a combination or modification of the references would be successful. References can only be combined or modified to obviate claims when there is a reasonable expectation of success. MPEP §2143.02; *see In re* Dow Chemical Co., 837 F.2d at 471, 473 (Fed. Cir. 1988) ("Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure."). Applicants respectfully assert that the Examiner has failed to show such a reasonable expectation of success for the combination of the '430 Patent and *Dinbergs*.

As discussed above, *Dinbergs* teaches that the use of TGF-β in the '430 Patent would not succeed in stimulating tissue growth, because sustained release of TGF-β does a better job of inhibiting proliferation than promoting it. And the '430 Patent teaches that cellular proliferation is what is needed to stimulate tissue growth to a detectable degree. Because the teachings of the '430 Patent and *Dinbergs* are incompatible, Applicants respectfully submit that the Examiner has failed to show why a skilled artisan would have reason to expect that the '430 Patent and *Dinbergs* combination would be successful. Accordingly, a prima facie case of obviousness has not been shown.

C. The proposed combination of the '430 Patent and *Dinbergs* does not take each prior art reference as a whole, but unacceptably parses the inventions for their parts

When determining whether an invention is obvious in view of the prior art, the Examiner must view each prior art reference as a whole. MPEP 2141.02. In addition, the MPEP and the Federal Circuit repeatedly warn against using an applicant's disclosure as a blueprint to reconstruct the claimed invention. For example, the MPEP states, "The tendency to resort to 'hindsight' based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art." MPEP § 2142; *see In re* Kotzab, 217 F.3d 1365, 1369 (Fed. Cir. 2000). Therefore, it is improper to base a determination of obviousness on the extraction and translocation of a detail from one invention to another.

The '430 Patent teaches the sustained release of growth factors to stimulate tissue growth. In this way, growth factors like TGF-β are released to stimulate the proliferation of tissues such as connective tissue, bone, cartilage, epidermis and dermis, blood, and other tissues. '430 Patent, col. 7, ll. 17-23. *Dinbergs* teaches that the sustained release of TGF-β will inhibit proliferation of cells. This inhibition of cell proliferation cannot be divorced from the '430 Patent's overarching goal of stimulating tissue growth.

Thus, for purposes of obviousness, the Examiner should consider every limitation of Applicant's claims. And when every limitation of Applicant's claims are considered, Applicant respectfully submits that the subject claims are not obvious in view of the combination of the '430 Patent and *Dinbergs*. For at least the reasons described above, Applicants respectfully submit that the combination of the '430 Patent and *Dinbergs* is improper. Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103 against the subject claims, and further request the timely issuance of a Notice of Allowance therefor.

VI. Rejection of Certain Claims Under 35 U.S.C. § 103 as Unpatentable Over the '430 Patent In View of the *Dinbergs* Reference in Further View of Other References

Claims 3, 5, 7, and 8 stand rejected as unpatentable over the '430 Patent in view of *Dinbergs* and in further view of additional references. Specifically, claim 3 was rejected in further view of *Scott-Burden* (Scott-Burden, et al., J. Cardiovasc. Pharmacol. 16 Suppl 4: S36-41 (1990)), (Office Action at 7); claims 5, 7, and 8 in further view of the '849 Patent (U.S. Pat. No.

5,935,849), (Office Action at 8); and claim 8 in further view of WO 94/23740 or WO 96/27657, (Office Action at 10). Applicants respectfully traverse.

Applicants' claims 3, 5, 7, and 8 depend either directly or indirectly from independent claim 1. All these dependent claims, which include all the limitations of claim 1, are allowable for at least the reasons cited above with respect to independent claim 1. *See* MPEP § 2143.03 ("If an independent claim is nonobvious uner 35 U.S.C. 103, then any claim depending therefrom is nonobvious."). Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103 against the claims 3, 5, 7, and 8, and further request the timely issuance of a Notice of Allowance.

VII. Rejection of Certain Claims Under 35 U.S.C. § 103 as Unpatentable Over the '430 Patent In View of the '849 Patent

Claims 24-27 and 32-34 stand rejected under 35 U.S.C. 103 as unpatentable over the '430 Patent in view of the '849 Patent. In asserting these rejections, the Examiner describes the alleged teachings of the '430 Patent as printed above in Section 4, and further states, in pertinent part:

> The '849 Patent teaches a method of making a tissue engineering scaffold such as bioartificial organ (BAO) using scaffold such as hydrogel or alginate or collagen (see col. 19, lines 22, col. 20, lines 42-36, summary of invention, in particular) covalently coupling to an inner matrix by a tether such as poly-d-lysine (see col. 18, line 30-35, in particular) coupling to matrix enhancing molecules such as RGD containing sequence (see col. 18, lines 36-51, in particular) or TGB beta and/or ascorbic acid (see col. 12, lines 56-67, in particular). The '849 patent teaches TGF beta is useful for inducing differentiation of fibroblast cells, and also as a growth inhibitor of keratinocytes and endothelial cells while ascorbic acid and TGBbeta1 increase collagen biosyntheis (see col. 12, lines 57-67, Table 1, in particular). The reference method further comprises providing cells such as fibroblast or endothelial cells attached within the tissue engineering scaffold (see col. 16, Table 1, Col. 19, line 29, in particular). The reference method is useful for implantation and controlling distribution of cells within the bioartificial organ (see claims of '849 patent).

(Office Action at 11-12.) Applicants respectfully disagree. Applicants also traverse many of the Examiner's statements concerning the teachings of the '849 Patent.

Applicants respectfully submit that the Examiner has not established a prima facie case of obviousness because the combination of the '430 Patent and '849 Patent has not been shown to teach or suggest each limitation of Applicants' independent claim 24, as required to obviate claims 24-27 and 32-34. MPEP § 2142.

In particular, the combination of the '430 Patent and '849 Patent has not been shown to teach or suggest "covalently coupling the matrix-enhancing molecule to the scaffold, wherein the matrix-enhancing molecule is present at a concentration sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell," as recited in Applicants' independent claim 24. As discussed above with respect to the § 102(b) rejection in Section 4, the '430 Patent has not been shown to teach this limitation. Nor has the '849 Patent been shown to supply this missing limitation. Nowhere has the '849 Patent been shown to discuss suitable concentrations of matrix-enhancing molecules, much less "a concentration sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell," as recited in Applicants' independent claim 24. Accordingly, the combination of the '430 Patent and '849 Patent has not been shown to teach each limitation of independent claim 24 and thus has not been shown to obviate claims 24-27 and 32-34. *See* MPEP § 2143.03.

For at least these reasons, Applicants respectfully request withdrawal of this rejection with respect to claims 24-27 and 32-34 because the Examiner has failed to establish a prima facie case of obviousness as required by MPEP § 2142. Applicants further request the timely issuance of a Notice of Allowance for claims 24-27 and 32-34.

VIII. Rejection of Certain Claims Under 35 U.S.C. § 103 as Unpatentable Over the '430 Patent In View of the '849 Patent and in Further View of *Dinbergs*

Claims 27 and 29 stand rejected under 35 U.S.C. 103 as unpatentable over the '430 Patent in view of the '849 Patent and further in view of *Dinbergs*. In asserting these rejections, the Examiner describes the alleged teachings of the '430 Patent as printed above in Section 4, the '849 Patent as printed above in Section 7, and *Dinbergs* as printed above in Section 5. (Office Action at 12-13.)

Applicants respectfully submit that the proposed combination is improper because the Examiner has not provided a sufficient teaching, suggestion, or motivation in the prior art to

make such a combination, as discussed above in Section 5. For at least the reasons discussed above in Section 5, Applicants respectfully submit that the combination of the '430 Patent, the '849 Patent, and *Dinbergs* is improper, and that such improper combination cannot properly be used to obviate the subject claims. Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. 103 against claims 27 and 29, and further request the timely issuance of a Notice of Allowance.

IX. Rejection of Certain Claims Under 35 U.S.C. § 103 as Unpatentable Over the '430 Patent In View of *Scott-Burden*

Claims 24 and 30 stand rejected under 35 U.S.C. 103 as unpatentable over the '430 Patent in view of *Scott-Burden*. In asserting these rejections, the Examiner describes the alleged teachings of the '430 Patent as printed above in Section 4, and further states, in pertinent part:

> The claimed invention in claim 30 differs from the reference only in that the method wherein the matrix-enhancing molecule is angiotensin II instead of TGF beta.
>
> Scott-Burden et al teach angiotensin II activates the synthesis of extracellular matrix such as glycopeptides and proteoglycans by smooth muscle cells and growth of smooth muscle cells (see abstract, in particular).

(Office Action at 14.) Applicants respectfully disagree and submit that the Examiner has not established a prima facie case of obviousness because the combination of the '430 Patent and *Scott-Burden* has not been shown to teach each limitation of Applicants' independent claim 24 as required to obviate claims 24 and 27. MPEP § 2142.

In particular, the combination of the '430 Patent and *Scott-Burden* has not been shown to teach or suggest the step of "covalently coupling the matrix-enhancing molecule to the scaffold, wherein the matrix-enhancing molecule is present at a concentration sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell," as recited in Applicants' independent claim 24. As shown above in Section 4, the '430 Patent has not been shown to disclose, teach, or suggest, either expressly or inherently, that "covalently coupling the matrix-enhancing molecule to the scaffold, wherein the matrix-enhancing molecule is present at a concentration sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell," as recited in Applicants'

independent claim 24. The Examiner relies on *Scott-Burden* for the teaching that "the matrix-enhancing molecule is angiotensin II instead of TGF beta." (Office Action at 14.) Accordingly, the Examiner has not shown that the combination of the '430 Patent and *Scott-Burden* teaches or suggests every limitation of Applicants' independent claim 24 and dependent claim 27; and thus the '430 Patent and *Scott-Burden* combination cannot be used to obviate Applicants' claims 24 and 27. *See* MPEP § 2143.03.

For at least these reasons, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103 against claims 24 and 27, and further request the timely issuance of a Notice of Allowance.

X. Rejection of Certain Claims Under 35 U.S.C. § 103 as Unpatentable Over the '430 Patent In View of WO 94/23740 or WO 96/27657

Claims 24 and 34 stand rejected under 35 U.S.C. 103 as unpatentable over the '430 Patent in view of WO 94/23740 or WO 96/27657. In asserting these rejections, the Examiner describes the alleged teachings of the '430 Patent as printed above in Section 4, and further states, in pertinent part:

> The claimed invention in claim 34 differs from the reference only in that the method wherein the scaffold is hyaluronic acid or polyethylene glycol polymers.
>
> The WO 94/23740 publication teaches a method for making a tissue engineering scaffold comprising coupling various matrix-enhancing molecules such as TGFβ or TGFβ2 covalently coupling to polyethylene glycol (See page 13, line 11, PEG-TGF-β conjugates, rhTGF- TGF-β2 (PEG5000) bridging page 13, in particular). The WO 94/23740 publication teaches the method of making a tissue engineering scaffold comprising coupling TGFβ to a polymer is useful for simulation of bone formation at a lower does (See abstract, in particular).
>
> The WO 96/27657 publication teaches a method for making a tissue engineering scaffold comprising coupling various matrix-enhancing molecules such as TGFβ (see page 10, claim 25 of WO 96/27657 publication, in particular) covalently coupled to a scaffold such as hyaluronic acid (see page 7, line 1, in particular) or collagen, or polyethylene oxide, or alginate, (See page 17, line 8, in particular). The WO 96/27657 publication teaches the growth factor is localized to desired target cell population and significantly less growth factor is needed to exert a biologic response (See abstract, in particular).

(Office Action at 15.) Applicants respectfully disagree and submit that the Examiner has not established a prima facie case of obviousness because the combination of the '430 Patent and WO 94/23740 or WO 96/27657 has not been shown to teach each limitation of Applicants' independent claim 24 as required to obviate claims 24 and 34. MPEP § 2142.

In particular, the combination of the '430 Patent and WO 94/23740 or WO 96/27657 has not been shown to teach or suggest the step of "covalently coupling the matrix-enhancing molecule to the scaffold, wherein the matrix-enhancing molecule is present at a concentration sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell," as recited in Applicants' independent claim 24. As shown above in Section 4, the '430 Patent has not been shown to disclose, teach, or suggest, either expressly or inherently, that "covalently coupling the matrix-enhancing molecule to the scaffold, wherein the matrix-enhancing molecule is present at a concentration sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell," as recited in Applicants' independent claim 24. The Examiner relies on WO 94/23740 or WO 96/27657 for the teaching that "the scaffold is hyaluronic acid or polyethylene glycol polymers." (Office Action at 14.) Accordingly, the Examiner has not shown that the combination of the '430 Patent and WO 94/23740 or WO 96/27657 teaches or suggests every limitation of Applicants' independent claim 24 and dependent claim 34; and thus the '430 Patent and WO 94/23740 or WO 96/27657 combination cannot be used to obviate Applicants' claims 24 and 34. *See* MPEP § 2143.03.

Furthermore, Applicants respectfully submit that the proposed combination is improper because the Examiner has not provided a sufficient teaching, suggestion, or motivation in the prior art to make such a combination. As shown above in Section 5, the '430 Patent emphasizes "healing or regrowth of normal tissue." *See, e.g.*, '430 Patent, col. 6, l. 53-col. 7, l. 5. Similarly, WO 94/23740 and WO 96/27657 emphasize cell growth and proliferation. *See, e.g.*, WO 94/23740 p. 20, ll. 8-12 ("Very highly significant proliferation of osteoblast-like cells was observed in the femur slides of mice treated at 3 μg with rTGF-β2 $(PEG\ 5000)_6$ OR rTGF-β2 $(PEG\ 5000)_4$ or rTGF-β2 $(PEG\ 35{,}000)_{1\text{-}3}$, as compared with controls."); WO 96/27657 at p.3, ll. 21-22 ("It is therefore an object of the invention to provide a cell and tissue growth substrate that stimulates long-term target cell growth."). In contrast, the present invention discloses, among

other things, increasing production of extracellular matrix while minimizing cell growth. Accordingly, one of ordinary skill attempting to increase production of extracellular matrix without increasing cell growth would not be motivated to combine the teachings of the '430 Patent and WO 94/23740 or WO 96/27657, because these references emphasizes increasing cell growth, in direct contrast to the present invention.

For at least these reasons, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. 103 against claims 24 and 34, and further request the timely issuance of a Notice of Allowance.

SUMMARY AND PETITION FOR ONE-MONTH EXTENSION OF TIME TO FILE THIS RESPONSE

In light of the above remarks, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections. Applicants further submit that the application is now in condition for allowance, and earnestly solicit timely notice of the same. Should the Examiner have any questions, comments, or suggestions in furtherance of the prosecution of this application, the Examiner is invited to contact the attorney of record by telephone, facsimile, or electronic mail.

Applicants' Response to this Office Action was due on January 29, 2006, along with the enclosed petition and fee for a two-month extension of time. As this Response is being filed on Monday, January 30, 2006, and in view of the fact that January 29, 2006 fell on a Sunday, a Petition for Two-Month Extension of Time to File this Response is included herein, along with check no. 953810 for the fee of $225.00 (small entity) under 37 C.F.R. 1.136(a). *See* MPEP § 710.05 "Period Ending on Saturday, Sunday, or a Federal Holiday."

Applicants believe that there are no additional fees due in association with this filing of this Response. However, should the Commissioner deem that any additional fees are due, including any fees for extensions of time, the Commissioner is authorized to debit Baker Botts L.L.P. Deposit Account No. 02-0383, Order Number 002376.1017, for any underpayment of fees that may be due in association with this filing.

Respectfully submitted,

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